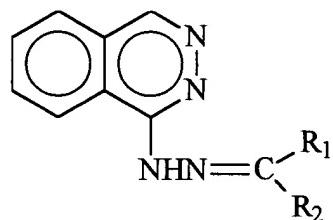


1 I claim

2 1. A method of improving the stability of a hydralazine composition during
3 manufacturing or storage comprising coupling an N-protecting group with hydralazine to
4 produce a compound having the formula:

5

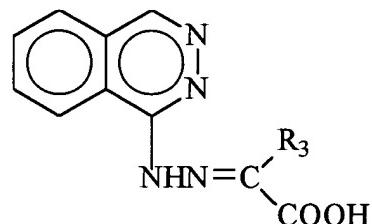


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7

8 or a compound having the formula:

9



10

11

12 where R_1 and R_2 are independently H, substituted or unsubstituted branched or straight
13 chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl,
14 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
15 unsubstituted alkylcycloalkyl, lower alkenyl or R_1 and R_2 together form part of a
16 substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms;
17 where R_3 is a branched or straight chain alkyl having from 1 to about 7 carbon atoms,
18 substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or
19 unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group
20 having the formula $(\text{CH}_2)_n\text{COOH}$ where n is from 1 to about 7; and

1 wherein said N-protecting group is removed from said compound after manufacturing or
2 storage.

3

4 2. The method of Claim 1 wherein the N-protecting group is acid-labile and is removed
5 from the hydralazine prior to administration of said compound to a patient.

6

7 3. The method of Claim 2 wherein the N-protecting group is plasma-labile and is
8 removed in plasma after administration of said compound to a patient such that the extent
9 and rate of appearance of hydralazine in the plasma is therapeutically similar to that of
10 hydralazine after administration of hydralazine under similar clinical conditions.

11

12 4. The method of Claims 1, 2 or 3 wherein R₁ and R₂ are independently a branched or
13 straight chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted
14 aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,
15 substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R₁ and R₂ together form
16 part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon
17 atoms.

18

19 5. The method of Claims 1, 2 or 3 wherein R₂ is H and R₁ is a branched or straight chain
20 alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted
21 or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
22 unsubstituted alkylcycloalkyl, lower alkenyl.

23

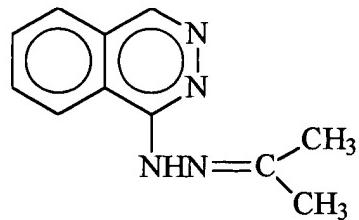
24 6. The method of Claim 4 wherein R₁ and R₂ are a branched or straight chain alkyl having
25 from about 1 to about 7 carbon atoms.

26

27 7. The method of Claim 5 wherein R₁ is a branched or straight chain alkyl having from
28 about 1 to about 7 carbon atoms.

1 8. The method of Claim 6 wherein said compound has the formula:

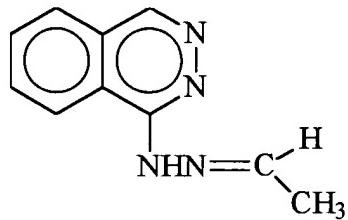
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3

4 9. The method of Claim 7 wherein said compound has the formula:

5

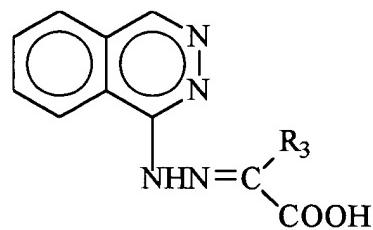


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7

8 10. The method of Claim 1 wherein said compound has the formula:

9



10

11 where R₃ is a branched or straight chain alkyl having from 1 to about 7 carbon atoms,
12 substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or
13 unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group
14 having the formula (CH₂)_nCOOH where n is from 1 to about 7.

15

1 11. The method of Claim 10 wherein R₃ is a branched or straight chain alkyl having from
2 1 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted
3 aralkyl, substituted or unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted
4 alkylcycloalkyl.

5

6 12. The method of Claim 10 wherein R₃ is a group having the formula (CH₂)_nCOOH
7 where n is from 1 to about 7.

8

9 13. The method of Claims 1, 2 or 3 wherein R₁ and R₂ are substituted or unsubstituted
10 aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,
11 substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R₁ and R₂ together form
12 part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon
13 atoms.

14

15 14. The method of Claims 1, 2 or 3 wherein R₂ is H and R₁ is substituted or unsubstituted
16 aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,
17 substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R₁ and R₂ together form
18 part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon
19 atoms.

20

21 15. The method of Claim 13 wherein R₁ and R₂ are substituted or unsubstituted aryl,
22 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
23 unsubstituted alkylcycloalkyl, lower alkenyl.

24

25 16. The method of Claim 13 wherein R₁ and R₂ together form part of a substituted or
26 unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms.

27

1 17. The method of Claim 14 wherein R₂ is H and R₁ is substituted or unsubstituted aryl,
2 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
3 unsubstituted alkylcycloalkyl, lower alkenyl or R₁ and R₂ together form part of a
4 substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms.

5

6 18. The method of Claim 14 wherein R₂ is H and R₁ is substituted or unsubstituted aryl,
7 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
8 unsubstituted alkylcycloalkyl, lower alkenyl.

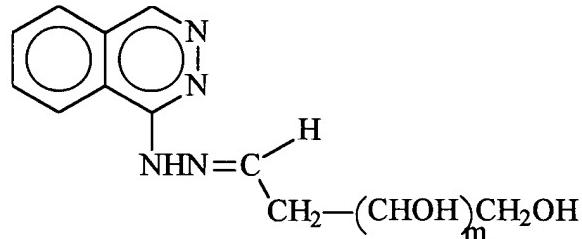
9

10 19. The method of Claims 1,2 or 3 wherein R₂ has the formula CH₂(CHOH)_mCH₂OH
11 where m is 2 or 3.

12

13 20. The method of Claim 19 wherein said compound has the formula:

14



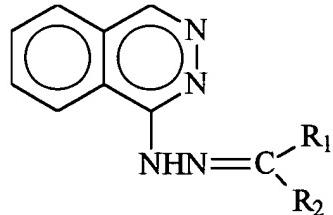
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16 where m is 2 or 3.

17

18 21. A compound having the formula:

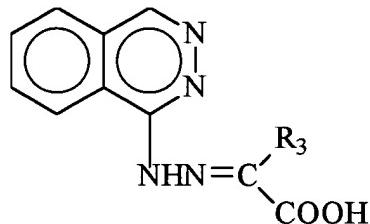
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2 or a compound having the formula:

3



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6 where R₁ and R₂ are independently H, branched or straight chain alkyl having from 2 to
 7 about 7 carbon atoms, unsubstituted aryl, substituted or unsubstituted cycloalkyl,
 8 substituted or unsubstituted aralkyl, substituted or unsubstituted alkylcycloalkyl, lower
 9 alkenyl; where R₃ is a branched or straight chain alkyl having from 2 to about 7 carbon
 10 atoms, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted
 11 or unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a
 12 group having the formula (CH₂)_nCOOH where n is from 3 to about 7; with the proviso
 13 that when R₁ is H or methyl, then R₂ is a branched or straight chain alkyl having from 2
 14 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted
 15 cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted
 16 alkylcycloalkyl, lower alkenyl.

17

18 22. The compound of Claim 21 wherein R₁ and R₂ are independently a branched or
 19 straight chain alkyl having from 2 to about 7 carbon atoms, substituted or unsubstituted
 20 aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl,
 21 substituted or unsubstituted alkylcycloalkyl, lower alkenyl or R₁ and R₂ together form
 22 part of a substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon
 23 atoms.

24

1 23. The compound of Claim 21 wherein R₂ is H and R₁ is a branched or straight chain
2 alkyl having from 2 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted
3 or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
4 unsubstituted alkylcycloalkyl, lower alkenyl.

5

6 24. The compound of Claim 23 wherein R₁ and R₂ are a branched or straight chain alkyl
7 having from about 2 to about 7 carbon atoms.

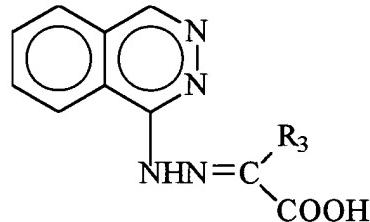
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9 25. The compound of Claim 23 wherein R₁ is a branched or straight chain alkyl having
10 from about 2 to about 7 carbon atoms.

11

12 26. The compound of Claim 21 wherein said compound has the formula:

13



14

15 where R₃ is a branched or straight chain alkyl having from 2 to about 7 carbon atoms,
16 substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or
17 unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group
18 having the formula (CH₂)_nCOOH where n is from 3 to about 7.

19

20 27. The compound of Claim 26 wherein R₃ is a branched or straight chain alkyl having
21 from 2 to about 7 carbon atoms, substituted or unsubstituted aryl, substituted or
22 unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, aralkyl, substituted or
23 unsubstituted alkylcycloalkyl.

24

1 28. The compound of Claim 26 wherein R₃ is a group having the formula (CH₂)_nCOOH
2 where n is from 3 to about 7.

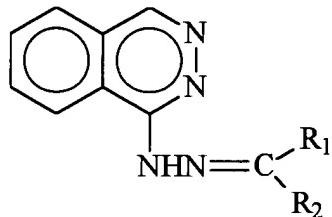
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4 29. The compound of Claim 21 wherein R₁ is substituted or unsubstituted aryl,
5 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
6 unsubstituted alkylcycloalkyl.

7

8 30. A particulate-free hydralazine composition comprising compound having the
9 formula:

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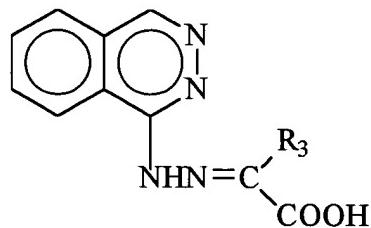


11

12

13 or a compound having the formula:

14



15

16

17 where R₁ and R₂ are independently H, substituted or unsubstituted branched or straight
18 chain alkyl having from 1 to about 7 carbon atoms, substituted or unsubstituted aryl,
19 substituted or unsubstituted cycloalkyl, substituted or unsubstituted aralkyl, substituted or
20 unsubstituted alkylcycloalkyl, lower alkenyl or R₁ and R₂ together form part of a

1 substituted or unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms;
2 where R₃ is a branched or straight chain alkyl having from 1 to about 7 carbon atoms,
3 substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or
4 unsubstituted cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group
5 having the formula (CH₂)_nCOOH where n is from 1 to about 7 in a pharmaceutically
6 acceptable salt or diluent.

7 31. The composition of Claim 30 wherein the composition is a liquid pharmaceutical
8 composition and the composition has been stored from about 18 to about 24 months after
9 completion of manufacturing and storage was initiated.

10

11 32. The composition of Claim 30 wherein the composition is an injectable formulation
12 and yellow-green particles do not form from 1 to about 2 months after storage 40° C and
13 after about 6 months storage at 25° C.

14

15 33. The composition of Claim 31 wherein the average number of particles of about 10
16 microns in the composition does not exceed 6,000.

17

18 34. The composition of Claim 31 wherein the average number of particles of about 25
19 microns in the composition does not exceed 600.

20

21 35. The composition of Claim 31 wherein no particles are visible.

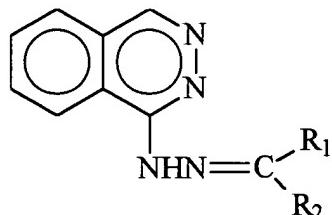
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23 36. The composition of Claim 31 wherein the average number of particles of about 10
24 microns in the composition does not exceed 6,000, the average number of particles of
25 about 25 microns in the composition does not exceed 600, and no particles are visible.

26

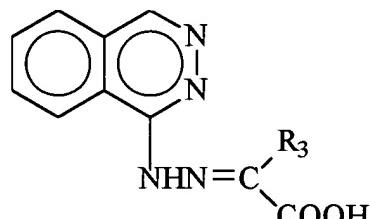
1 37. A metal ion-free hydralazine composition comprising a compound having the
2 formula:

3



4

5 or a compound having the formula:



6

7 where R₁ and R₂ are independently H, branched or straight chain alkyl having from 1 to
8 about 7 carbon atoms, substituted or unsubstituted aryl, substituted or unsubstituted
9 cycloalkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted
10 alkylcycloalkyl, lower alkenyl or R₁ and R₂ together form part of a substituted or
11 unsubstituted cycloalkyl having from about 4 of about 7 carbon atoms; where R₃ is a
12 branched or straight chain alkyl having from 1 to about 7 carbon atoms, substituted or
13 unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted
14 cycloalkyl, aralkyl, substituted or unsubstituted alkylcycloalkyl or a group having the
15 formula (CH₂)_nCOOH where n is from 1 to about 7; in a pharmaceutically acceptable salt
16 or diluent; and wherein said compound in said hydralazine composition does not complex
17 with metal ions.

18

19 38. The composition of Claim 37 wherein the metal ions are selected from the group
20 consisting of Cu⁺², Fe⁺² and Fe⁺³.

21